

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference RLL-414WO	FOR FURTHER ACTION		See item 4 below
International application No. PCT/IB2004/002511	International filing date (<i>day/month/year</i>) 04 August 2004 (04.08.2004)	Priority date (<i>day/month/year</i>) 05 August 2003 (05.08.2003)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant RANBAXY LABORATORIES LIMITED			

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|---|
| <input checked="" type="checkbox"/> | Box No. I | Basis of the report |
| <input type="checkbox"/> | Box No. II | Priority |
| <input type="checkbox"/> | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> | Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> | Box No. VI | Certain documents cited |
| <input type="checkbox"/> | Box No. VII | Certain defects in the international application |
| <input type="checkbox"/> | Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Date of issuance of this report 06 February 2006 (06.02.2006)
Facsimile No. +41 22 740 14 35	Authorized officer <div style="text-align: center; font-weight: bold;">Idhir Britel</div> Telephone No. +41 22 338 70 60

PATENT COOPERATION TREATY

REC'D 31 JAN 2005	
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From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/IB2004/002511

International filing date (day/month/year)
04.08.2004

Priority date (day/month/year)
05.08.2003

International Patent Classification (IPC) or both national classification and IPC
C07C213/06, C07C215/46, C07C223/02, C07C217/62

Applicant
RANBAXY LABORATORIES LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1b/s(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/002511

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/002511

**Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or
Industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-55
	No: Claims	56-57
Inventive step (IS)	Yes: Claims	
	No: Claims	1-55
Industrial applicability (IA)	Yes: Claims	1-57
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V.

1. The following documents have been taken into consideration:

- D1: WO 01/96279 A (SANOL ARZNEI SCHWARZ GMBH ; MEESE CLAUS (DE)) 20 December 2001 (2001-12-20)
D2: EP-A-0 957 073 (SANOL ARZNEI SCHWARZ GMBH) 17 November 1999 (1999-11-17)
D3: WO 01/35957 A (SANOL ARZNEI SCHWARZ GMBH ; MEESE CLAUS (DE)) 25 May 2001 (2001-05-25)
D4: WO 94/11337 A (KABI PHARMACIA AB ; JOHANSSON ROLF ARNE (SE); MOSES PINCHAS (SE); NILV) 26 May 1994 (1994-05-26)
D5: WO 98/43942 A (HARALDSSON MARTIN ; PHARMACIA & UPJOHN AB (SE); RINGBERG ERIK (SE); EM) 8 October 1998 (1998-10-08)

2. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 56-57 is not new in the sense of Article 33(2) PCT.

The compound of formula IV according to claim 56 has been disclosed in the document D2 (see intermediate A paragraphs [0028] and [0039]), D3 (see compound 4 on page 24) and D3 (see page 12, line 35 and page 13 line 10).

The compound of formula V according to claim 57 has been disclosed in the documents D5 (see examples 17.1, 17.2, 29.1, 30 and claim 19 (second compound)).

The process according to claim 1 relates to the preparation of N, N-diisopropyl-3-(2-hydroxy-5-hydroxyphenyl)-3-phenylpropanamine (compound of formula I) by benzylation of N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine (tolterodine), followed by oxidation of the 5-methyl group to the corresponding **aldehyde** of formula IV, followed by the reduction of the aldehyde to the 5-hydroxymethyl derivative of formula V which is debenzylated to the desired compound of formula I.

The subject-matter of claim 1 is novel vis-à-vis D1-D7 (Article 33(2) PCT).

3. The closest prior art is considered to be D4 which discloses a process for the

preparation of the compound of formula (I) by direct oxidation of the 5-methyl group to the corresponding 5-hydroxymethyl derivative of formula V which is debenzylated to the desired compound of formula I (see step g of claim 10).

The direct reduction of a 5-carbomethoxymethyl derivative to the corresponding 5-hydroxymethyl derivative of formula V followed by a debenzylation step to the desired compound of formula I has been also disclosed in D4 (see pages 12 and 13).

The present process differs from the process disclosed in step (g) of D4 due to the fact that the oxidation of the 5-methyl group to the corresponding CH_2OH group is not carried directly. In the present process said 5-methyl group is first oxidized to the corresponding **aldehyde** of formula IV, followed by the reduction of the aldehyde to the 5-hydroxymethyl derivative of formula V.

The problem to be solved by the present invention may be regarded as the provision of an improved process for the preparation of the metabolite of tolterodine of formula (I).

However, the present solution is regarded as obvious in the light of the common general knowledge of the man skilled in the art. In the absence of any convincing experimental evidence or argument, the present process cannot be regarded as advantageous over the direct oxidation of the CH_3 group or the direct reduction of the ester group disclosed in D4.

Therefore, the subject-matter of the present application is not considered to fulfil the requirements of Art. 33(3)PCT.